Anti-tumor Activity of PEG-rHuIL-10 (AM0010) in Renal Cancer alone and in combination with anti-PD1

Aung Naing[1], Kyriakos P. Papadopoulos[2], Karen A. Autio[3], Patrick A. Ott[4], Manish Patel[5], Deborah J. Wong[6], Gerald S. Falchook[7], Shubham Pant[8], Melinda Whiteside[9], Drew R Rasco[2], Amita Patnaik[2], John B. Mumm[9], Ivan H. Chan[9], Johanna C. Bendell[10], Todd M. Bauer[10], Rivka R. Colen[1], David S. Hong[1], Peter Van Vlasselaer[9], Gail L Brown[9], Nizar M. Tannir[1], Martin Oft[9#] and Jeffrey R. Infante[10]

[1]MD Anderson Cancer Center, [2] START Center for Cancer Care, San Antonio, TX; [3] Memorial Sloan-Kettering Cancer Center, New York, NY; [4] Dana-Farber Cancer Institute, Boston, MA; [5] Sarah Cannon Research Institute/Florida Cancer Specialists, [6]University of California Los Angeles (UCLA), Los Angeles, CA, [7] Sarah Cannon Research Institute at HealthONE, Denver, CO, [8] Oklahoma University, [9] ARMO BioSciences, Redwood City CA; [10] Sarah Cannon Research Institute / Tennessee Oncology, PLLC; # These authors contributed equally

Background and Purpose

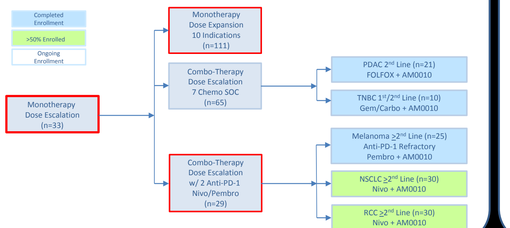
Background

IL-10 is regarded as an anti-inflammatory cytokine but it is also essential for the cytotoxicity and proliferation of antigen activated CD8 T cells. Activation of the T cell receptor induces the expression of IL-10 receptors and PD-1 on CD8 T cells. This provides the mechanistic rationale for combining AM0010 and anti-PD1 for the treatment of cancer pts. Tolerability and anti-tumor activity of AM0010 alone and in combination with chemotherapies or immune checkpoint inhibitors was explored in a multi-basket phase 1 clinical trial.

Methods

Pts with advanced renal cell cancer (RCC) were treated with AM0010 alone (daily SC) or in combination with Pembrolizumab (q3wk IV). Tumor responses were monitored following irRC. Immune responses were measured by analysis of serum cytokines, activation of blood derived T cells, peripheral T cell clonality.

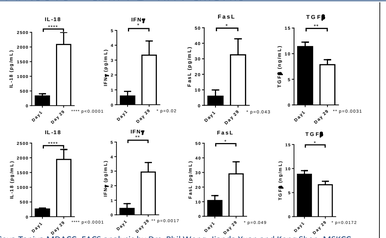
Study Design

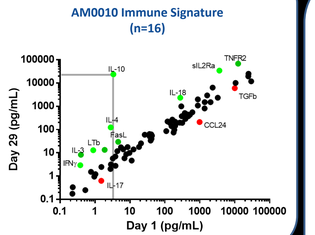


Immune Activation by PEG-IL-10 or AM0010 + anti-PD-1in Patients

AM0010 - immune activation signature

- AM0010 treatment (20µg/kg) induced a comprehensive immune signature in the serum of patients
  - Th1 cytokines: IFNγ , IL-18
  - Dendritic cell stimulation: IL-4, GM-CSF
  - Growth factor for memory CD8+ T cells: IL-7
  - CD8+ T cell activity: FasL, LT-b
  - Immune suppression: TGF-β
- Th17 cytokines were reduced
- Other inflammatory cytokines were not significantly altered
- IL-10 immune activation signature is activated in all patients – with or without anti-PD-1
- AM0010 increases Phospho-STAT3 in tumor infiltrating CD8+ T cells





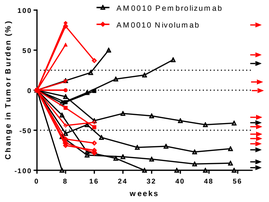
Serum cytokine assays by Myriad RBM; IHC by Dr. Scott Rodig DFCI and Cr. Coya Tapiya MDACC; FACS analysis by Drs. Phil Wong, Jianda Yuan and Kong Shen, MSKCC

Conclusion and Outlook

- **Durable responses in RCC both with AM0010 monotherapy**
  - **4 of 15 evaluable patients (27% ORR)**
- **Increased response rate in AM0010 + Pembrolizumab (n=8)**
  - **Very durable, mPFS 9.95 months**
  - **2 PR, 2 CR in 8 patients (50%ORR)**
- **Monotherapy and anti-PD-1 combination is well tolerated up to 18 months**
- **Sustained Th1 / CD8+ T cell mediated immune activation**
  - Increase in Th1 cytokines and products of CD8+ T cells
    - Not enhance by anti-PD-1
  - Increase of activated tumor infiltrating CD8+ T cells
  - Increase of activated, Lag-3+, PD-1+ CD8+ T cells
  - Expansion of rare, previously not detected T cell clones in the blood
    - Correlating with response
    - Not significantly enhanced by anti-PD-1
- **Sustained Th1 / CD8+ T cell mediated immune activation**

Outlook: AM0010 + Nivolumab compared to AM0010 + Pembrolizumab - Preliminary Results

- 10 patients with RCC treated with AM010 (20µg/kg qd) and Nivolumab (3mg/kg q2w) had an tumor asessment
- The combination was well tolerated at 20µg/kg AM0010 – no increase of irAEs
- RCC (n=10): ORR 33%, DCR 70% at 8 weeks, 1 delayed response
- Preliminary results with AM0010 + nivolumab appear comparable to pembrolizumab results

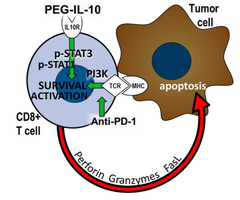


Mechanism of Action

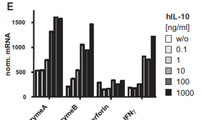
- CD8+ T cells require a T cell receptor signal (TCR) AND a confirmatory cytokine stimulation for activation and SURVIVAL in the tumor
- Tumor antigen recognition by CD8+ T cells (TCR) induces the IL-10 receptor and PD-1 on CD8+ T cells
  - IL-10 activates CD8+ T cells and provides positive feedback ("Cytotoxic License")
  - PD-1 inhibits the TCR signal in CD8+ T cells, provides negative feedback ("Immune Checkpoint")

PEGylated IL-10 (AM0010) induces the activation and survival of intra-tumoral, tumor reactive CD8+ T cells through phosphorylation of the transcription factors STAT1 and STAT3. Pegylation of IL-10 aims to ensure that the essential survival pathway for intra-tumoral CD8+ T cells is activated without interruptions.

- In-vitro treatment of human CD8+ T cells with IL-10 increases expression of cytotoxic enzymes and their antigen specific cytotoxicity
- IL-10 rescues CD8 T cells from activation induced cell death (AICD) and induces STAT3 phosphorylation in CD8+ T cells.



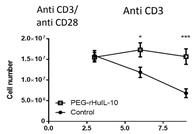
IL-10 → Cytotoxicity of CD8 T cells



CD8+ T cells were isolated from a peripheral blood mononuclear cells, treated with increasing concentrations of hIL-10 after anti-CD3 stimulation and mRNA was analyzed for the expression of cytotoxicity mediating enzymes (Mumm et al. Cancer Cell 2011)

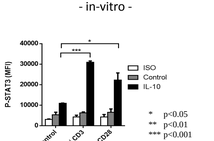
IL-10 inhibits Activation Induced Cell Death and Activates STAT3 in CD8+ T cells

Activation induced cell death



Phospho-STAT3 in CD8+ T cells

- in-vitro -



CD8+ T cells, isolated from human PBMCs were activated with anti-CD3 and anti-CD28, cultured with or without hIL-10 followed by anti CD3 stimulation. Cell numbers were measures.
CD8+ T cells, isolated from human PBMCs were activated with anti-CD3 or anti-CD3 + anti-CD28, followed by stimulation with hIL-10. Phosphorylated STAT3 was quantified by FACS analysis in response to IL-10 stimulation

* p<0.05
** p<0.01
*** p<0.001

Results

AM0010 Monotherapy

- Patient self-administered daily doses of 20 µg/kg AM0010 SC.
- Grade3/4 TrAE were anemia (17%), thrombocytopenia (17%); Grade 2 TrAEs included fatigue (67%), rash (67%), fever (50%), chills (50%) and pruritis (33%).

AM0010 + anti-PD-1

- Patients self-administered daily doses of 20 µg/kg AM0010 SC, received Pembrolizumab 2 mg/kg q3w IV.

Treatment related adverse events – AM0010 + pembrolizumab cohorts

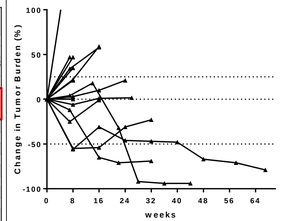
Combination	AM0010 - Pembro							
	Grade 1		Grade 2		Grade 3		Grade 4	
AM0010 Dose	10µg/kg	20µg/kg	10µg/kg	20µg/kg	10µg/kg	20µg/kg	10µg/kg	20µg/kg
Number of Patients	N=13	N=6	N=13	N=6	N=13	N=6	N=13	N=6
Hematopoietic AEs								
Anaemia	1 (8%)		3 (23%)	2 (33%)	2 (15%)	1 (17%)		
Neutropenia			1 (8%)			1 (17%)		
Thrombocytopenia	3 (23%)		3 (23%)		2 (15%)	1 (17%)		
Non-hematopoietic AEs								
Anorexia	3 (23%)	1 (17%)	3 (23%)					
Cough	2 (15%)							
Dehydration			2 (15%)					
Diarrhea	2 (15%)							
Dysgeusia	2 (15%)		1 (8%)					
Fatigue	2 (15%)	2 (33%)	6 (46)	2 (33%)				
Fever		3 (50%)						
Hemoptysis						1 (17%)		
Injection site reaction	2 (15%)	2 (33%)						
Insomnia	1 (8%)							
Malaise								1 (17%)
Nausea	1 (8%)	3 (50%)	1 (8%)					
Pneumonitis		1 (17%)	2 (15%)					
Pruritis	2 (15%)	2 (33%)	1 (8%)		1 (8%)			
Rash - generalized		2 (33%)		1 (17%)				
Rash - maculopapular	2 (15%)	2 (33%)	1 (8%)	1 (17%)	2(15%)			
Shortness of breath		1 (17%)		2 (33%)				
Weakness								
Lab values								
ALT / AST increase	1 (8%)					2 (33%)		
Hyperglycemia						1 (17%)		
Hypertriglyceridemia	2 (15%)		1 (8%)		1 (8%)	1 (17%)		
Hypokalemia					1 (8%)			
Hyponatremia					1 (8%)			

Table includes all patients with a G1-4 TrAEs according to NCI-CTCAE (1 event was not coded).
Patients in the AM0010+Pembro cohort received 10 or 20 µg/kg AM0010 daily and 2mg/kg Pembrolizumab every three weeks

AM0010 Monotherapy

- 15 patients with RCC treated at 20 µg/kg had disease evaluation
- 4 patients had a partial response (PR)
- 2 PR had a late response
- The median progression free survival (mPFS) was 3 months

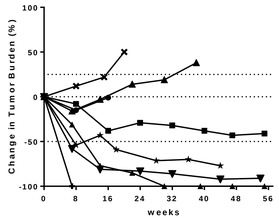
RCC with AM0010 Monotherapy



AM0010 + Pembrolizumab

- 8 patients with RCC treated at 10 or 20 µg/kg AM0010 with Pembrolizumab (2mg/kg q3w) had disease evaluation
- 4 patients had an objective tumor response, 2 had a PR, 2 and a CR
- The median progression free survival was 9.95 months

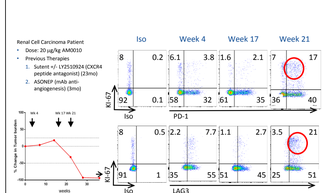
RCC with AM0010 + Pembrolizumab



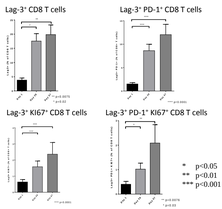
	AM0010	AM0010 + Pembro	AM0010 + Nivo
Objective responses	4 PR (n=15)	2 PR 2 CR (n=8)	3 (n=9) in progress
ORR	27% (n=15)	50% (n=8)	
mPFS (months)	3.0	9.95	
mOS (months)	9.8	NR (>14)	
Prior Therapies, median (range)	3 (0-7)	2.5 (0-4)	

PD-1+ LAG-3+ KI-67+ CD8+ T cells in response to AM0010 Monotherapy

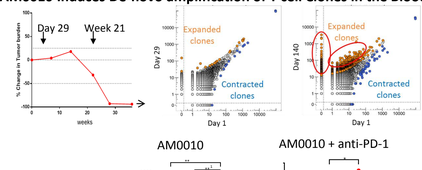
AM0010 monotherapy induces KI67+ PD-1+ / LAG3+ CD8+ T cells coinciding with tumor shrinkage

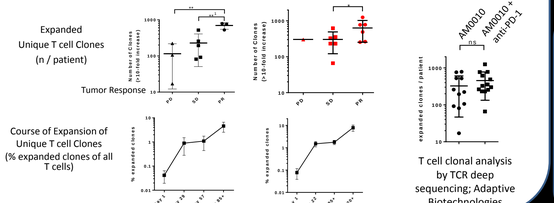


AM0010 monotherapy induces expansion of KI67+ PD-1+ LAG3+ CD8+ T cells



AM0010 Induces De-novo amplification of T cell Clones in the Blood





T cell clonal analysis by TCR deep sequencing; Adaptive Biotechnologies

Information

SPONSORS

AM0010 is being developed by ARMO BioSciences.

REFERENCES

1.Mumm et al. Cancer Cell 2011; Emmerich et al. Cancer Research 2012
2.Fridman, Pages et al. NRI 2012; Oft. CIR 2014 (Reviews)
3.Topalian, Hodi et al. NEJM 2012; Tumeh, Harview et al. Nature 2015

CONTACT INFORMATION

The pdf of this poster is at http://www.armobio.com/news-events/publications For more information on this trial, go to clinicaltrials.gov (NCT02009449) or contact martin.oft@armobio.com phone: 1-650-779-5075